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Study ID: CMO-US-ID-0528

Title: Development of a New Critical Pathway for Treatment of Acute Bacterial Skin and Skin Structure Infections

Statistical Analysis Plan: 09 May 2018

[redacted]

Statistical Analysis Plan

Version 1.0 Dated: 09May2018

ENHANCE: Development of a New Critical Pathway for Treatment of Acute Bacterial Skin and Skin Structure Infections

Protocol Number: CMO-US-ID-0528 v 6.0 Dated: 03MAR2017

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Statistical Analysis Plan - Approval

ENHANCE: Development of a New Critical Pathway for Treatment of Acute Bacterial Skin and Skin Structure Infections

Protocol:
Number: CMO-US-ID-0528
Version: 6.0
Date: 03MAR2017

Statistical Analysis Plan
Version: 1.0
Date: 09MAY2018

This Statistical Analysis Plan has been reviewed and approved by the individuals listed below.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABSSSI	acute bacterial skin and skin-structure infections
AE	adverse event
AIDS	acquired immune deficiency syndrome
BMI	body mass index
BP	blood pressure
CCI	Charlson Comorbidity Index
CCR	cost:charge ratio
CI	confidence interval
CRF	case report form
CSR	clinical study report
ED	emergency department
FAS	full analysis set
GFR	Glomerular filtration rate
g/dL	grams per deciliter
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ICU	intensive care unit
LOS	length-of-stay
LTC	long-term care
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MCS	mental component score
MOS	medical outcomes study
mEq/L	milliequivalents per liter
mmHg	milliliter of mercury
mmol/L	millimolar
mg/dL	milligrams per deciliter
MRSA	Methicillin-resistant *Staphylococcus aureus*
OPAT	outpatient parenteral antibiotic therapy
PICC	peripherally inserted central catheter
PCS	physical component score
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
SF	short-form
SIRS	Systemic Inflammatory Response Syndrome
SNF	skilled nursing facility
US	United States
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment Questionnaire

[redacted]

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1.0 Introduction

This statistical analysis plan (SAP) outlines the planned analysis for data collected within Allergan study CMO-US-ID-0528, entitled "Development of a New Critical Pathway for Treatment of Acute Bacterial Skin and Skin Structure Infections". This SAP applies to the protocol, Version 6.0, dated March 03th, 2017, and provides a description of methods for handling the data.

This pragmatic trial has been developed to assess a new critical pathway for the treatment of acute bacterial skin and skin-structure infections (ABSSSI); it will include the use of guideline-based criteria to identify patients eligible for outpatient parenteral antibiotic therapy (OPAT), and, for those who meet these criteria, the use of dalbavancin — a novel, single-dose, long-acting, second generation lipoglycopeptide indicated for the treatment of ABSSSI caused by susceptible strains of Gram-positive bacteria.

2.0 Study Objectives

2.1 Primary Objective

The primary objective of this study is to estimate the difference in infection-related total admitted hospital days during initial care (the date of enrollment to 10-14 days) and follow-up (30 days after initial care) comparing ABSSSI patients receiving care before implementation of the new critical pathway and after implementation.

2.2 Secondary Objectives

The secondary objectives of this study are to estimate the difference in the following outcomes during initial care (the date of enrollment to 14 days) and follow-up (30 days after initial care) comparing ABSSSI patients receiving care before implementation of the new critical pathway and after implementation:

- Total admitted hospital days during initial care and follow-up
- Infection-related major surgical interventions that required operating room time during initial care and follow-up
- Infection-related hospitalizations during initial care and follow-up
- Infection-related hospitalizations during initial care and follow-up that resulted in admission to Intensive Care Unit (ICU)
- All cause hospitalizations in the 30 days post discharge from the hospital
- Infection-related emergency department (ED) visits during initial care and follow-up
- Infection-related outpatient healthcare visits during initial care and follow-up
- Use of a peripherally inserted central catheter (PICC) line or central line to administer antibiotic therapy during initial care and follow-up
- Infection-related healthcare visits due to PICC line or central line used to administer antibiotic therapy during initial care and follow-up

[redacted]

- Response to treatment at end of treatment visit
- Serious adverse events (SAEs) during initial care and follow-up
- Patient satisfaction with care (patient reported or completed by a caregiver if the patient cannot complete)
- Patient work and productivity loss (patient reported or completed by a caregiver if the patient cannot complete)
- Patient Health-related Quality of Life (HRQoL) (patient reported or completed by a caregiver if the patient cannot complete)

3.0 Study Design

This study will employ a "pre-post" pragmatic design, which will consist of both a pre-period, or an observational baseline period, and a post-period, or an interventional period. The pre-period and post-period will consist of independent groups of patients. During the pre-period, the site will implement the first component of the critical pathway through implementation of guideline-based criteria to identify patients admitted to the hospital, obtain informed consent, and monitor enrolled subjects. The site will initiate treatment for ABSSSI with "usual care," defined as site- or physician-specific antibiotic treatment of ABSSSI with coverage for a known or suspected Gram-positive infection (e.g., vancomycin, linezolid, and daptomycin) to each study patient who meets all inclusion and exclusion criteria. Blinding of treating physician to patient enrollment in the study during the pre-period will ensure unbiased provision of usual care. During the post-period, for all patients who provide informed consent and are subsequently enrolled, each participating site will additionally implement the second component of the new critical pathway, use of dalbavancin, at the point of care in the hospital or other designated site to each study patient who meets all inclusion and exclusion criteria.

For both periods of interest, patient follow-up spans the period beginning on the day of study enrollment and ends 44 days thereafter, which incorporates an initial care period of 14 days (reflecting the 10–14-day period during which most antibiotics are anticipated to be required for care of ABSSSI) and a subsequent "follow-up" period of 30 days. Study measures will be collected as described in the protocol and will be based on medical records, unless otherwise indicated.

A schedule of assessments is provided in Appendix A. Follow-up visits will be scheduled for approximately 48-72 hours after enrollment (both periods), 10-14 days after enrollment (both periods), and 44 days after enrollment (both periods). Any additional visits to the visit schedule given in Appendix A will be at the discretion of the patient and treating physician.

The duration of the study was not predetermined; it is dependent on the time required to enroll the necessary number of eligible patients (43 patients per time period; 86 patients enrolled in all).

[redacted]

4.0 Study Measures

4.1 Baseline Characteristics

The following baseline characteristics will be collected:

- **Demographic data**: Age (in years, derived and described in Appendix B), gender, ethnicity, race, employment status, and location patient presents from (e.g. from home, long-term care [LTC], skilled nursing facility [SNF], nursing home).
- **Comorbidities**: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes with/without complications, renal disease, moderate or severe liver disease (Child-Pugh Class B and C), any malignancy (including leukemia and lymphoma), metastatic solid tumor, cancer (active, remitted/cured), alcohol/drug abuse/illicit needle use, malnutrition, human immunodeficiency virus (HIV), other immuno-compromising conditions, altered mental status, lymphedema or chronic venous stasis, and peripheral vascular disease.
- **Charlson Comorbidity Index (CCI)**: A derived variable based on the presence/absence of the comorbidities specified above. The formula by which the CCI is calculated is detailed in Appendix C.
- **Infection type**: Cellulitis/erysipelas, wound infection, major cutaneous abscess
- **Infection and clinical characteristics during the initial assessment at the hospital and end of treatment visit**:
    - Lesion size and location
    - Pain and tenderness associated with the lesion
    - Fever (>100.4˚F; >38.0˚C; or site-specific definition)
    - *Systemic inflammatory response syndrome* (SIRS) (see Appendix B)
    - Blood pressure (BP, in mmHg)
    - Total white blood cell count ($x10^9$/L)
    - Hemoglobin (g/dL)
    - Sodium (mmol/L)
    - Glucose (mg/dL)
    - Serum creatinine (mg/dL)
    - C-reactive protein (mg/dL)
    - Rapid microbial assay
    - Microbiological culture type (i.e. blood, wound swab, urine) and results thereof
    - Presence of recurrent infection and/or any ABSSSI infections in the prior 6 months
- **Utilization of healthcare services in prior 3 months**: Hospitalizations and primary reason, surgical interventions and primary

[redacted]

reason, admission to the ICU and primary reason, ED visits or other outpatient visits (e.g., infusion center and physician's office) and primary reason, use of dialysis, use of any medications for chronic diseases and specifically use of an antibiotic medication, prior antibiotic treatment failure (determined by discontinuation of treatment due to worsening or recurrent ABSSSI or the occurrence of an adverse event related to the antibiotic), and receipt of wound care for the presenting infection.

4.2 Primary Outcome

The primary outcome (i.e., infection-related total number of days spent in hospital) will be assessed during the 44-day period of interest, including the initial-care period (i.e., beginning on the date of enrollment and ending 14 days thereafter) and the follow-up period (the 30-day period following initial care).

4.3 Secondary Outcomes

Secondary outcomes will be assessed during initial care (the date of enrollment to day 14) and/or follow-up (30 days after initial care), and include:

Measure	Definition	Period of Assessment
Total admitted hospital days	Total length of stay (LOS) of all hospitalizations during the 44 days of the study (including initial hospitalization)	Initial care and follow-up
Infection-related major surgical interventions that required operating room time	Number of all, unexpected and expected infection-related major surgical interventions that required operating room time	Initial care and follow-up
Infection-related hospitalizations	Number of infection-related hospitalizations	Initial care and follow-up
Infection-related hospitalizations that resulted in admission to ICU	Number of infection-related hospitalizations resulting in admission to the ICU.	Initial care and follow-up
All-cause hospitalizations in the 30 days following discharge from the initial hospitalization	Number of all hospitalizations for patients after initial hospitalization discharge	Overall, including Initial care and follow-up
Infection-related ED visits	Number of all, unexpected and expected infection-related ED visits	Initial care and follow-up

Measure	Definition	Period of Assessment
Infection-related outpatient healthcare visits (e.g., physicians' office visits, ED visits, infusion center visits, home health visits)	Number of all, unexpected and expected infection-related outpatient healthcare visits, generated for all patients and repeated by site.	Initial care and follow-up
Use of PICC line or central line to administer antibiotic therapy	Number of PICC line or central line placement for antibiotic therapy	Initial care and follow-up
Infection-related healthcare visits (e.g., hospitalizations, ED visits, other outpatient visits) due to PICC line or central line used to administer antibiotic therapy	Number of all, unexpected and expected infection-related healthcare visits due to PICC line or central line used to administer antibiotic therapy	Initial care and follow-up
Response to treatment at end of therapy visit	Response to treatment will be defined through an assessment of erythema and the absence of fever at 10-14 days and will be categorized as a complete response, partial response, or failure.	Initial care
Serious adverse events (SAEs)	Number of events, number of patients and percentage of patients experiencing SAEs as described in protocol	Initial care and follow-up
Patient satisfaction with care	Summarize patient satisfaction with care (reported by patient, questionnaire provided in protocol). This will be completed by a caregiver if the patient cannot complete.	Follow-up
Patient work and productivity loss	Number of days with lost/reduced productivity, as measured through the Work Productivity and Activity Impairment	Follow-up

[redacted]

Measure	Definition	Period of Assessment
	(WPAI) questionnaire. This will be completed by a caregiver if the patient cannot complete.	
Patient HRQoL	Patient reported, as measured through the SF-12[1](short-form), with acute recall (1-week recall). This will be completed by a caregiver if the patient cannot complete.	Initial care (in person) and follow-up (in person). Change scores calculated for initial care

Healthcare resource usage during the three months prior to the study will be based on examination of the patient's medical records.

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[redacted]

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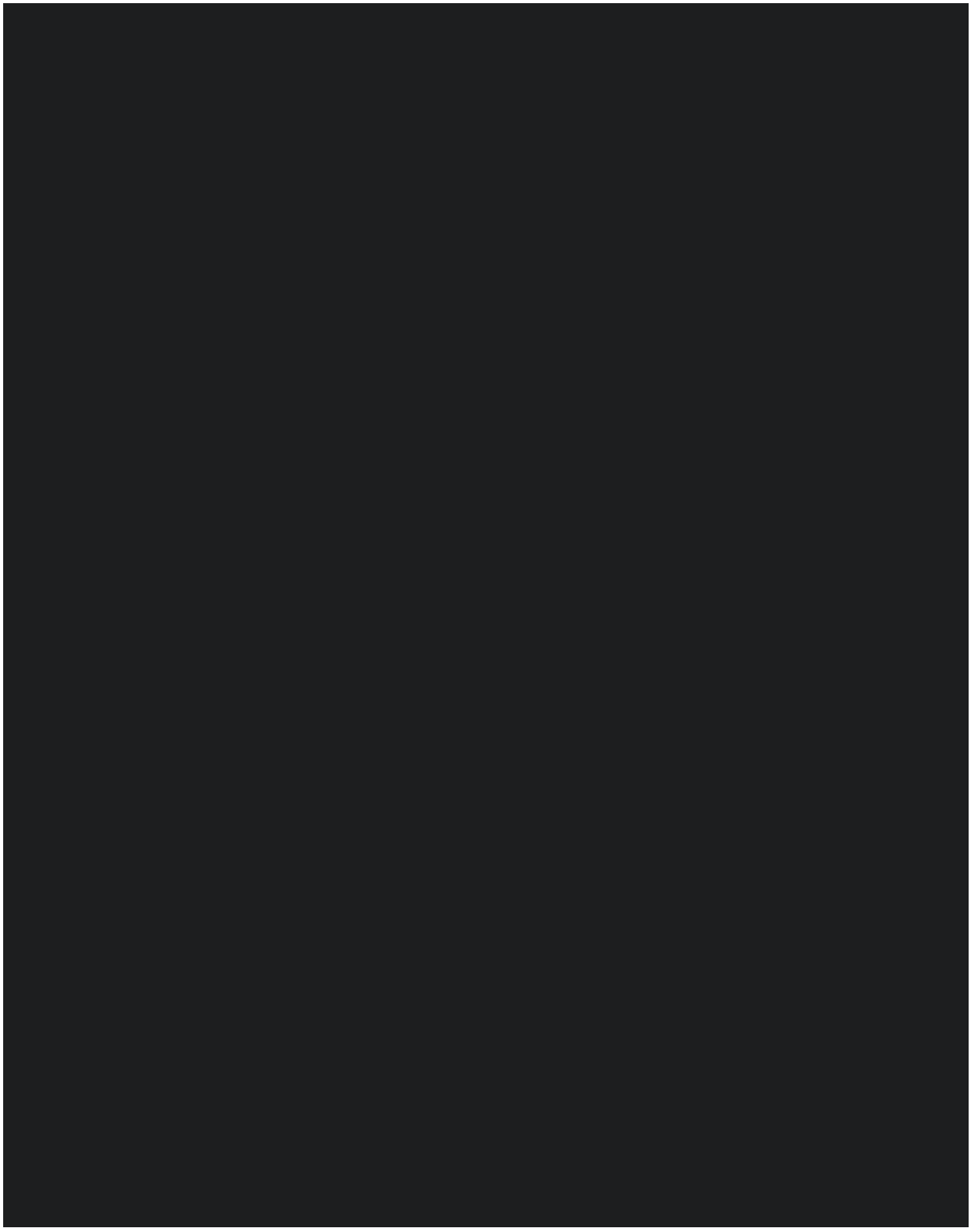
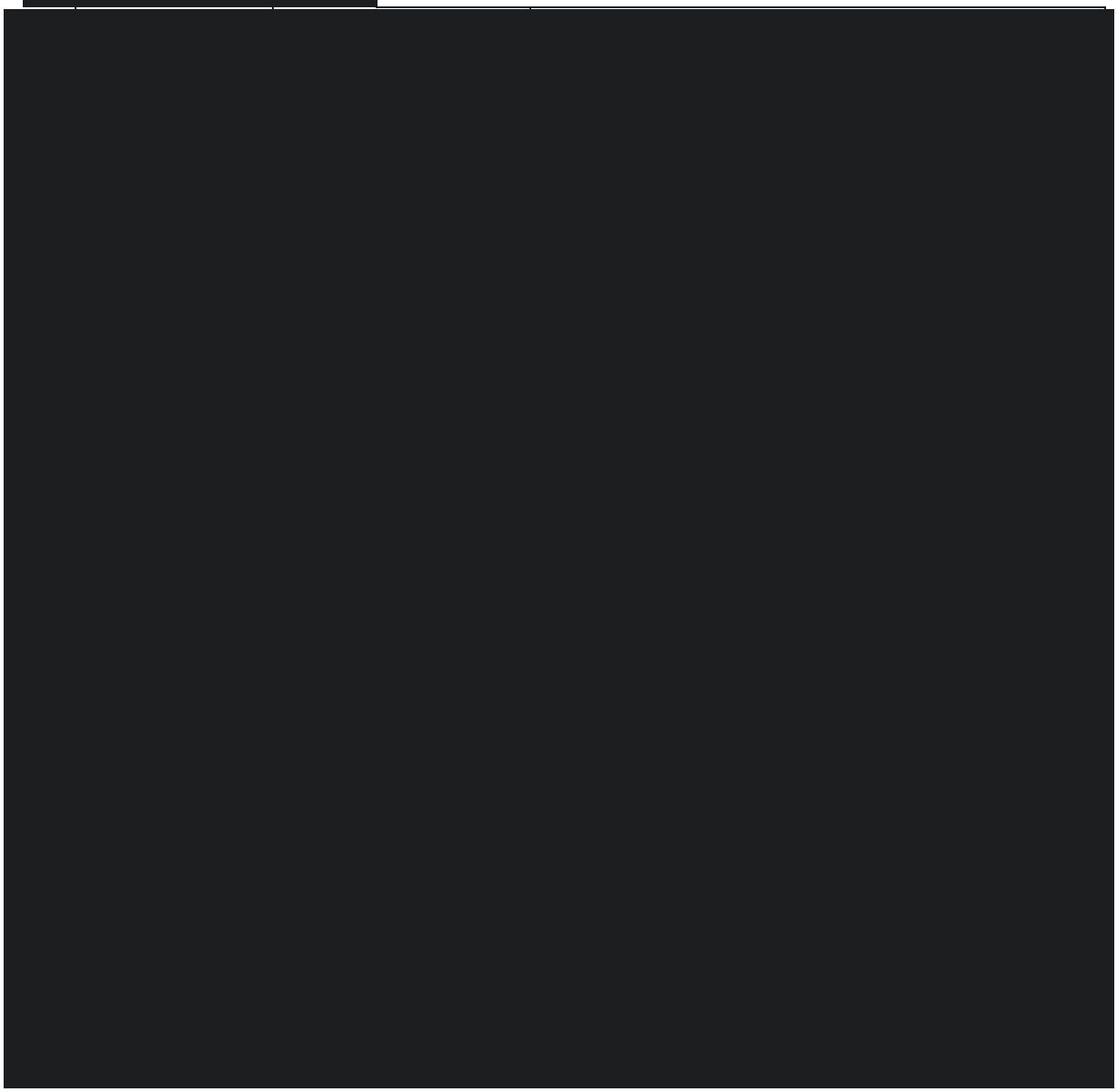
[redacted]



[redacted]



4.6 Safety

At each visit, patients will be queried regarding adverse events (AEs) and SAEs, and medication errors that occurred since the previous visit. Specifically, patients will be asked to volunteer information with a non-leading question such as, "How do you feel since your last visit?" Study site personnel will record all pertinent information in the patient's case report form (CRF), as described in details in the protocol.

5.0 Changes in the Protocol Specified Analyses

Infection characteristics described in the protocol including hyperglycemia (>120mg/dL blood glucose or site-specific definition), thrombocytopenia

(<150,000 platelet count or site-specific definition), acidosis (<7.35 pH of the blood or site-specific definition or described in medical chart), hyponatremia (<135 mEq/L blood sodium or site-specific definition), uremia (as described in medical chart), and anemia (14-18 g/dL hemoglobin for men or 12-16 g/dL hemoglobin for women or site-specific definition) will not be derived from laboratory values or reported in analysis.

The protocol specifies that the Mann-Whitney U test will be utilized for comparison of continuous variables in analyses. However, it was later determined that the t-test offers better power and easier inference in most moderate to large sample size situations where assumptions of the t-test are not grossly violated. Therefore, the t-test where possible and reverting to non-parametric alternatives only in special circumstances. The rationale for this change is as follows:

- The sample size estimate in the protocol is based on a t-test. As the study is powered for a t-test, it would be most appropriate to use a t-test if possible.
- T-tests are generally equally or more powerful than Mann-Whitney U tests if the sample size is moderate or large, even if the normality assumption is not met[2]. Non-parametric tests may not have adequate power to detect differences for the sample.
    - Per Lumley *et al.*[2]: "In small samples most statistical methods do require distributional assumptions, and the case for distribution-free rank-based tests is relatively strong. However, in the large data sets typical in public health research, most statistical methods rely on the Central Limit Theorem, which states that the average of a large number of independent random variables is approximately Normally distributed around the true population mean. It is the normal distribution of the average that underlies the validity of the t-test…"
    - The sample size is sufficient to meet this criterion even if the data are right-skewed. This assumption will be reassessed if the data are extremely non-normal.
- Results from the Mann-Whitney U test may not be easily described nor have valuable clinical meaning. The Mann-Whitney U test is a comparison of medians only if the distributions of the two groups are shaped identically and heavily skewed. In all other situations, the Mann-Whitney U test is a comparison of the sum of ranks for the two groups. It would not be appropriate to provide mean or median point estimates and corresponding CIs in this situation as they are likely to conflict with the probability resulting from the Mann-Whitney U test. An example of such a situation is provided in Lumley *et al.*[2]
- All assumptions for the t-test will be carefully checked. If there are major violations to the assumptions for the t-test, including a strong departure from normality, the Mann-Whitney U test or another appropriate non-parametric method will be used as applicable.

Similarly, the protocol specifies that difference in proportions will be analyzed by Fisher's exact test. However, it was later determined the use of a chi-square test to compare categorical variables accompanied with asymptotic 95% CIs on differences in proportions. All assumptions of the chi-square test will be carefully checked. If the expected value for any cell reported in applicable tables is <5, Fisher's exact test will be used as appropriate.

6.0 Statistical Plan and Methods

As the data are analyzed, some deviations from expectations and/or assumptions will become apparent (e.g., missing data, distributional assumptions, and small sample sizes in some subgroups of interest). In instances where these deviations would make the proposed analyses inappropriate/infeasible and/or difficult to interpret, modifications to the analysis plan will be made accordingly, and noted in the final report.

6.1 General Considerations

6.1.1 Analysis populations

Enrolled Set

The enrolled set consists of all patients who have signed informed consent and met all study eligibility criteria. Data will be summarized on disposition and baseline characteristics. Output will be summarized by study period (pre-period vs. post-period). All data listings will be reported for the enrolled set unless specified in Section 5.2.

Full Analysis Set

The full analysis set (FAS) population consists of all enrolled patients. Additionally, patients in the pre-period must receive at least one dose of antibiotics and patients in the post-period must receive at least one dose of dalbavancin for inclusion. All patients in the pre-period and post-period will be analysed. Data will be summarized by study period.

6.1.2 Sample size

An estimated 86 patients are anticipated to be enrolled at one US site. The sample size was initially estimated for a two-sided hypothesis test (two-sample equal-variance t-test) with a significance level of 0.05 comparing total hospital time (number of days) between the pre- and post-periods with 80% power. Assuming an average hospital length of stay of 4.0 days (inclusive of all enrolled subjects), with a standard deviation of 3.0 days, and a 2 day reduction in length of stay between the pre- and post-periods, it was estimated that 37 subjects in each arm of the trial (total enrollment of 74) would be required to demonstrate a mean reduction in hospital stay of 2 day. The final enrollment, including adjustments for attrition came to 86 subjects (43 patients in each period).

The average length of stay and variance for the site was determined after an estimated 25 subjects were enrolled in the pre-period. The sample size was confirmed with the interim analysis and the enrollment of 86 patients will be targeted.

6.1.3 Rounding

Means and medians will be rounded to one decimal more than that which the variable was recorded. Standard deviations will be rounded to two decimals more than that which the variable was recorded.

Percentages will be rounded to the nearest integer. Percentages for responses to a variable will only include patients with non-missing data, i.e. the denominator will be the number of patients with non-missing data.

P-values will be reported to three decimal places. Probabilities that are <0.001 will be presented as "<0.001."

6.1.4 Handling of outliers

Outliers will be examined using descriptive statistics, making sure that the minimum and maximum of the variable of interest are not unusually small or large and that the standard deviation seems appropriate for the data. If an outlier(s) is detected (e.g; more than 3 SD from the mean), the accuracy of the entry of the data point(s) will be verified (when possible) and corrected if appropriate.

Potential outliers will be identified prior to any statistical analysis. The effect of the any outliers on the analysis will determined by the statistician. Outliers will be included in or excluded from the statistical analyses as appropriate.

6.1.5 Handling of missing and/or incomplete data

Patients will be missing specific data points for a variety of reasons. With the exception of validated instruments, missing values for a given time point will not be imputed and analyses will be conducted using an observed case approach. For validated instruments, missing items will be handled according to instructions from the relevant scoring manuals. Missing dates will be handled with an observed case approach.

6.1.6 Interim analysis

As documented in the protocol, Version 6.0, there was an interim analysis of data to check the sample size assumptions based on approximately 25 enrolled pre-period patients. A separate report was completed on the interim analysis. No further interim analysis is planned. The output that was produced for the interim analysis is denoted in the table shells with a ∫ following the title.

6.1.7 Subgroup analyses

Currently no subgroup analyses are planned for this study. If applicable, analyses will be repeated for subgroups of interest.

6.1.8 Statistical software

All analyses will be performed by statisticians/data analysts, in accordance with Good Programming Practices guidelines, and will follow the statistical analysis plan outlined in this document, including the corresponding table shells referenced herein. All analyses will be performed using [redacted] or later to format tables and listings. Table, listing and figure output will be generated and delivered as Adobe Acrobat (PDF) files.

6.1.9 Quality Control

All output will be validated and/or QC'd according to Mapi standard operating procedures. Output tables and figures will be double programmed and undergo statistical review prior to being sent to Allergan.

6.2 Statistical Methods

Descriptive analyses will be performed as follows: for continuous variables, patient counts, percentages, means, 95% confidence intervals (CI) of the means, standard deviations (SD), medians, first (25th percentile) and third (75th percentile) quartiles, minima and maxima, and number missing (where applicable) will be reported. For categorical variables, patient counts and percentages for each category, as well as number missing (where applicable), will be reported. Where applicable, summaries for continuous variables will include frequencies and percentages for discrete categories (e.g., number of ED visits: 0, 1, 2, and so forth).

For applicable categorical variables of baseline characteristics (including demographics, infection characteristics at baseline and the day 10-14 follow-up visit, comorbid conditions reported at baseline, and prior healthcare resource utilization within past 3 months), the pre-period will be compared with the post-period using chi-square tests or Fisher's exact tests, as appropriate. Differences in proportions of the pre-period and post-period and their corresponding asymptotic 95% confidence interval (CI) will be reported, where applicable. For applicable continuous variables, two-sided Student's t-tests and Mann-Whitney U tests will be used where normality assumptions have, and have not, been met, respectively. Where applicable, differences in descriptive statistics, proportions, and corresponding 95% CI will also be provided between the pre- and post-periods.

Hypothesis testing is specified for outcomes in Section 6.2.4. All statistical testing, if done, will be at the significance level of 0.05. Other outcomes will be analyzed by descriptive analyses and by number of incidences where applicable. Planned analyses are presented in Section 6.2.4.2 for secondary

outcomes. All planned hypothesis testing and any unplanned deviation from hypothesis testing for secondary outcomes will be purely exploratory, as adequate power will not be present to determine statistical significance. There will be no adjustments made for multiple comparisons.

6.2.1 Patient Disposition

The number and percentage of enrolled and FAS patients, number and percentage of patients who complete the study, and number and percentage of patients who discontinue from the study and reason for withdrawal will be summarized in tables for all patients. This information will also be reflected in a data listing including the patient's enrollment date, early discontinuation or study completion date, and date of death, if applicable. Patients who are excluded from the enrolled set due to not meeting inclusion or exclusion eligibility criteria will be summarized in listings.

Although tables and listings will not reflect screen failures captured with enrollment logs, the clinical study report (CSR) text will address the approximate number of screen failures and the most common reasons for screen failure.

6.2.2 Demographic and Baseline Characteristics

All demographic data will be summarized in tables and listings for the enrolled and FAS populations. Descriptive statistics will be summarized for age (in years), height at baseline (in cm), weight at baseline (in kg) and body mass index (BMI) at baseline (in kg/m^2). Patient counts and percentages will be summarized for age (e.g., <20 years, 20-29 years, 30-39 years, etc.), race/ethnicity, gender, employment status (e.g., employed, full time, part time, unemployed), admission source (e.g., from home, LTC, SNF, nursing home), and insurance information. This information will be captured in listings with date of birth.

All baseline characteristics for comorbid conditions will be summarized for the FAS population by patient counts and percentages in tables and include the following measures: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, moderate or severe liver disease (Child- Pugh Class B and C), hemiplegia, lymphedema / chronic venous stasis, diabetes mellitus (with and without end-organ damage), moderate to severe chronic kidney disease (e.g., actual measurement and GFR, estimated measurement and GFR, unknown measurement), leukemia and remission status, lymphoma and remission status, metastatic solid tumor and remission status, alcohol abuse, drug abuse including illicit needle use, protein calorie malnutrition, immuno-compromising conditions such as HIV, acquired immune deficiency syndrome (AIDS), receiving ≥20 mg Prednisone daily (or therapeutically equivalent steroid), receiving TNF inhibitors, receiving any other immune modulating medication including biologics, and receiving chemotherapy. The Charlson Comorbidity

Index will be derived and described by descriptive statistics. All data will be reflected in listings.

Healthcare resource utilization within the 3 months prior to study enrollment will be reported in tables for the FAS population. Number of patients and percentages of occurrences (e.g., none, any, 1, 2, ≥3) and primary reasons for the following will be reported for hospitalizations, admissions to the ICU, surgical interventions, and ED or outpatient visits. Descriptive statistics will also be presented for these variables. Additionally, number of patients and percentages of coded diagnoses terms will be reported for hospitalizations and admissions to the ICU and number of patients and percentages for specified surgical procedures. The number and percentages of patients with minor and major surgical procedures will be displayed. The table will also reflect the number and percentages of patients with dialysis use, prior medications used for chronic diseases, antibiotics taken within 3 months of study enrollment (any and described by prescription reason and treatment failure and described by prescription reason), and wound care for the presenting infection. Listings for hospitalizations will capture the type of visit, primary reason for visit, primary diagnosis (coded and verbatim), admission date and time, discharge date and time, ICU admissions for hospitalizations, and discharge disposition. Prior antibiotic medications will be reported in a listing and will include start date and end date, medication named (coded and verbatim), reasons for prescription, dose with units and frequencies, route, and reason for discontinuation.

6.2.3 Infection Characteristics at Baseline and Follow-up

Infection characteristics at baseline and the day 10-14 follow-up visit will be reported in tables for the FAS population. As applicable, patient counts and percentages will be summarized for primary infection type, purulent drainage from primary lesion, any pain with primary lesion, tenderness of primary lesion, primary lesion location, primary lesion size (75cm^2 – 150 cm^2, ≥150 cm^2) number of additional lesions (e.g., 0, 1, 2, ≥3), fever, SIRS (met i.e., ≥2 criteria present, by individual criteria, and by number of criteria met), and recurrent/ABSSSI infection in prior 6 months. Descriptive statistics will be summarized for primary lesion size and pain on a 10-point scale. Differences in infection characteristics between the pre- and post-period will be assessed using statistical significance testing. All of the aforementioned variables will be reflected in listings.

6.2.4 Outcomes

6.2.4.1 Primary Outcomes

Primary Outcome: Infection-related Total Admitted Hospital Days

Infection-related total admitted hospital days will be calculated by two methods for the FAS population. First, LOS will be calculated by inpatient only stays and second, LOS will be calculated by inpatient stays including time spent in prolonged observation status (>1 day). Descriptive statistics for the primary

outcome will be shown in a table by initial care, follow-up, and overall for the pre-period and post-period, and depicted graphically overall using box plots. Patient counts and percentages will be given for the primary outcome (e.g., 0 day, 1 day … > 5 days). Descriptive statistics in the table will be repeated by all patients and patients who complete the study for comparison.

The primary analysis will consist of Hypothesis testing using a two sided (two sample equal-variance) t-test, with a significance level of 0.05, comparing the difference in total time (in days) spent in hospital between the pre- and post-periods. Violations of assumptions for the t-test in the data will be checked for. An appropriate alternative method will be selected if a major violation to an assumption is present, such as the Mann-Whitney U test[2]. Overall differences in descriptive statistics between the pre- and post-periods for infection-related total admitted hospital days will be reported.

Because the baseline characteristics of the pre-period may differ from those of the post-period, a secondary analysis using a multivariate regression analyses, specifically a generalized linear mixed model (GLMM), [redacted]. As the outcome is expected to be heavily right skewed, the number of hospital days will be modeled assuming a negative binomial distribution with log link. If the model does not converge or fit, an alternate distribution will be selected. This model will assume mutual independence between the sites. Similar to above, the multivariate analysis will be completed for the primary outcome for inpatient stays only as well as including time spent under observation, as well as for all patients and patients who complete the study for comparison.

Clinically relevant baseline characteristics of interest for the adjusted analysis (as described in Section 4.1) including the following variables: age, gender (Male, Female), race (White/Caucasian, Black or African American, Other), employment status (Full-Time, Part-Time, None), insurance plan type (Private commercial plan, Government funded, Uninsured, Other), Charlson Comorbidity Index, lesion surface area (<75cm cm2, =>75 cm2 – 150 cm2, >150 cm2), infection type (Wound infection, Cellulitis/erysipelas, Abscess), prior health resource use (Yes, No, Unknown), prior antibiotic treatment failure (Yes, No, Unknown), presence of SIRS criteria (<2 or >=2), presence of recurrent infection in prior 6 months (Yes, No, Unknown), any health resource use in prior 3 months (Yes, No, Unknown), as well as is patient was immunocompromised (Yes, No, Unknown). Patients will be defined as immunocompromised if they have evidence of any of the following at baseline: Connective tissue disease, diabetes mellitus, leukemia, or malignant lymphoma. These characteristics will be selected for the GLMM model by use of stepwise selection with the [redacted] procedure and a statistical significance level of <0.1. Categorical variables will be collapsed where possible. The primary predictor variable will be a pre/post-period indicator, and potentially other selected characteristics will be forced into the model based on clinical rationale and distributions observed in the data (specifically

imbalance between the pre- and post-periods); as it is assumed that patients enrolled in each site will be correlated, a generalized linear mixed model (GLMM) will be generated. The GLMM will adjust for correlated data among patients at sites by using a RANDOM statement in analyses. The Kenward and Roger method for approximating degrees of freedom will be taken for inference on the fixed effects. The final model results will be presented in a table.

6.2.4.2 Secondary Outcomes

Secondary Outcomes: Total Admitted Hospital Days

Total admitted hospital days will be calculated by two methods for the FAS population. First, LOS will be calculated by inpatient only stays and second, LOS will be calculated by inpatient stays including time spent in prolonged observation status (>1 day). The total admitted hospital-days will be assessed using a similar approach described for the primary analysis and will include all hospital stays. Tables will reflect descriptive statistics for total admitted hospital days and depicted graphically overall using box plots. Hypothesis testing will be performed by a two sided (two sample equal-variance) t-test, with a significance level of 0.05, comparing the difference in total time (in days) spent in hospital between the pre- and post-periods. Violations of assumptions for the t-test in the data will be checked for. An appropriate alternative method, such as the Mann-Whitney U test[2], will be selected if a major violation to an assumption of the t-test is present. Overall differences in descriptive statistics between the pre- and post-periods for total admitted hospital days will be reported.

Secondary Outcomes: Infection-Related Major Surgical Interventions that Required Operating Room Time

Infection-related major surgical interventions that required operating time will be displayed in tables by initial care, follow-up, and overall for the pre-period and post-period for the FAS population. Patient counts and percentages will be reported for no, any, expected, and unexpected surgical interventions. Differences in proportions between the pre- and post-period will be analyzed by a chi-square test or Fisher's exact test, as appropriate, and given with asymptotic 95% CIs.

Secondary Outcomes: Infection-Related Hospitalizations

Infection-related hospitalizations will be displayed in tables by initial care, follow-up, and overall for the pre-period and post-period for the FAS population. Patient counts and percentages will be reported for none, any, 1, 2, and ≥3 infection-related hospitalizations. Differences in proportions between the pre- and post-period will be analyzed by a chi-square test or Fisher's exact test, as appropriate, and given with asymptotic 95% CIs.

Secondary Outcomes: Infection-Related Hospitalizations that Resulted in Admission to ICU

Infection-related hospitalizations that resulted in admission to ICU will be displayed in tables by initial care, follow-up, and overall for the pre-period and

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post-period for the FAS population. Patient counts and percentages will be reported for none, any, 1, 2, and ≥3 infection-related hospitalizations that resulted in admission to ICU. Differences in proportions between the pre- and post-period will be analyzed by a chi-square test or Fisher's exact test, as appropriate, and given with asymptotic 95% CIs.

Secondary Outcomes: All-Cause Hospitalizations in the 30 Days Post-Discharge from the Hospital

All-cause hospitalizations in the 30 days post-discharge from the hospital will be displayed in tables for the pre-period and post-period for the FAS population. Patient counts and percentages will be reported for none, any, 1, 2, and ≥3 all-cause hospitalizations in the 30 days post-discharge from the hospital. Differences in proportions between the pre- and post-period will be analyzed by a chi-square test or Fisher's exact test, as appropriate, and given with asymptotic 95% CIs.

Secondary Outcomes: Infection-Related ED Visits

Infection-related ED visits will be displayed in tables by initial care, follow-up, and overall for the pre-period and post-period for the FAS population. Patient counts and percentages will be reported for none, any, 1, 2, and ≥3 infection-related ED visits. These categories will be repeated for all, expected, and unexpected ED visits. Differences in proportions between the pre- and post-period will be analyzed by a chi-square test or Fisher's exact test, as appropriate, and given with asymptotic 95% CIs.

Secondary Outcomes: Infection-Related Outpatient Healthcare Visits

Infection-related outpatient healthcare visits will be displayed in tables by initial care, follow-up, and overall for the pre-period and post-period for the FAS population. Patient counts and percentages will be reported for none, any, 1, 2, and ≥3 infection-related outpatient healthcare visits. These categories will be repeated for all, expected, and unexpected outpatient healthcare visits. Differences in proportions between the pre- and post-period will be analyzed by a chi-square test or Fisher's exact test, as appropriate, and given with asymptotic 95% CIs.

Secondary Outcomes: Use of PICC Line or Central Line to Administer Antibiotic Therapy

Use of PICC line, central line or no line to administer antibiotic therapy will be displayed in tables by initial care, follow-up, and overall for the pre-period and post-period for the FAS population. Patient counts and percentages will be presented. Differences in proportions between the pre- and post-period will be analyzed by a chi-square test or Fisher's exact test, as appropriate.

Secondary Outcomes: Infection-related Healthcare Visits Due to PICC Line or Central Line Used to Administer Antibiotic Therapy

Infection-related healthcare visits due to PICC line or central line used to administer antibiotic therapy will be displayed in tables by initial care, follow-

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up, and overall by the pre-period and post-period for the FAS population. Patient counts and percentages will be reported for none, any, 1, 2, and ≥3 infection-related outpatient healthcare visits. These categories will be repeated for all, expected, and unexpected outpatient healthcare visits. Differences in proportions between the pre- and post-period will be analyzed by a chi-square test or Fisher's exact test, as appropriate, and given with asymptotic 95% CIs.

Secondary Outcomes: Response to Treatment at End of Treatment Visit

Response to treatment at end of treatment visit will be a derived variable and further detail for the derivation is given in Appendix B. Response to treatment at end of treatment visit (complete, partial, failure) will be displayed in tables for the pre-period and post-period for the FAS population. Patient counts and percentages will be presented. Differences in proportions between the pre- and post-period will be analyzed by a chi-square test or Fisher's exact test, as appropriate.

Secondary Outcomes: Serious Adverse Events

Serious adverse events will be reported in a table as presented in section 6.2.7. No formal hypothesis testing will take place.

Secondary Outcomes: Patient Satisfaction with Care

Descriptive statistics for the patient satisfaction questionnaire will be reported within a table by the pre-period and post-period for the FAS population. No scoring or formal hypothesis testing will take place. A listing will display the date of visit the assessment occurred, questions answered, and the response to each question for each patient.

Secondary Outcomes: Patient Work and Productivity Loss

Descriptive statistics for the WPAI questionnaire will be reported in a table by the pre-period and post-period for the FAS population. Summaries will describe the distribution of scores derived at day 14. Scores will be calculated and summarized following the WPAI Score Guidelines (see Appendix D). A listing will display the date of visit the assessment occurred, component scores (absenteeism, impairment while working, overall work impairment, activity impairment), questions answered, and the response to each question for each patient.

Secondary Outcomes: Patient HRQoL

Descriptive statistics for the SF-12 will be reported within a table by the pre-period and post-period for the FAS population. Summaries will describe the distribution of scores derived at baseline and day 14, as well as the distribution of changes in scores from baseline. Scores will be calculated and summarized following the SF-12 scoring manual (see Appendix E). A listing will display the date of visit the assessment occurred, component scores (mental health and physical), questions answered, and the response to each question for each patient.

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6.2.5 Clinical Assessments

Vital signs including temperature (°C), method of collection of temperature, heart rate (beats per minute), respiratory rate (breaths per minute), systolic BP (mmHg), diastolic BP (mmHg), height (cm), weight (kg) and BMI (kg/m^2)

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will be summarized at baseline and the 48-72 hours after enrollment follow-up visit (post-period only).

Height is collected in both inches (in) and centimeters (cm) and will be reported in centimeters in the analysis. If height is reported in inches then it will be converted as follows:

Height (cm) = reported value (inches) * 2.54

Weight is collected in both pounds (lbs) and kilograms (kg) and will be reported in kilograms in the analysis. If weight is reported in pounds then it will be converted as follows:

Weight (kg) = reported value (lbs) * 0.4536

Temperature is collected in both degrees Celsius and Fahrenheit and will be reported in degrees Celsius in the analysis. If temperature is reported in degrees Fahrenheit then it will be converted as follows:

Temperature (°C) = (reported value (°F) – 32) / 1.8

Clinical assessments will be summarized with descriptive statistics for baseline and the day 10-14 visit by the pre-period and post-period for the FAS population. Values will be summarized in tables and listings, and in listings, reported with the visit date and change form baseline for follow-up values.

6.2.6 Antibiotic Treatments and Concomitant Medications

Concomitant medications taken three months prior to study start will be coded using the WHODRUG dictionary, Version B2 201609 or later, and the number and percentage of patients will be summarized in tables. Antibiotic usage during the study will also be coded using the WHODRUG dictionary, Version B2 201609 or later, and summarized in tables. The most current WHODRUG dictionary will be used at the time of analysis. These prior non-antibiotic medications used for chronic conditions will be reported in listings, including the medication name (coded), reason for prescription, route, and start date and end date. All medications will be summarized using descriptive statistics by the pre-period and post-period for the FAS population. For post-period patients, discharge to complete care in an outpatient setting on the same day Dalvance was provided and reasons for not being discharged to an outpatient setting will be summarized by patient counts and percentages.

6.2.7 Safety Assessments

The reporting period for adverse events (AEs) begins from the time of the signing of the Patient Authorization throughout the patient's enrollment in the study. AE information will be collected in an ongoing fashion through patient reporting AEs to their healthcare provider.

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All AEs will be coded and summarized by the pre-period and post-period for the FAS population by system organ class and preferred term based on the MedDRA coding dictionary Version 20.0 or later; the most current MedDRA coding dictionary will be used at the time of analysis. AEs will be summarized as related to treatment if there is evidence to suggest a causal relationship between the study drug (any antibiotic given for ABSSSI from enrollment, including the pre-period or post-period) and adverse event, and as not related if there is no evidence to suggest a causal relationship between the study drug and adverse event. For severity, the most severe case of an AE by a patient will be reported, with order of most severity as: Severe>Moderate>Mild.

A listing of adverse events will also be given for each patient and will include the reported term, seriousness, severity, relationship to treatment, action taken with medication, event outcome, and date for each event reported.

6.2.8 Laboratory and Microbiology

All laboratory and microbiological assessments will be summarized for baseline and follow-up visit in tables with descriptive statistics by the pre-period and post-period for the FAS population. Laboratory results will be reported for the scheduled baseline and day 10-14 visit. The first microbiology result for each patient at baseline and follow-up, respectively, will be summarized for each time period. Where more than one unit is collected within analysis, values will be converted to a common unit and displayed for analysis. Laboratory conversions to standard international units are reported in the table below:

Laboratory Unit	**Standard International Unit**	**Factor**
Sodium mEq/L	Sodium mmol/L	x1
Potassium mEq/L	Potassium mmol/L	x1
Bicarbonate mEq/L	Bicarbonate mmol/L	X1

A listing of laboratory and microbiological assessments will also be given for each patient and will include the time period the assessment was taken (e.g., initial care, follow-up), date of assessment, laboratory test, reported laboratory value, reported laboratory unit, specimen type, method of collection, if any isolated were grown from the specimen, the organism grown, if this organism was tested for susceptibility, what antibiotics were used for susceptibility, the level of susceptibility (sensitive, resistant, intermediate, indeterminate) and the minimum inhibitory concentration (MIC) with corresponding unit.

6.2.9 Healthcare Costs

Total costs of care for each study patient over the 44-day period of interest will be estimated by multiplying estimates of utilization of healthcare services collected during the conduct of this study by corresponding unit costs. Unit

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costs will include: cost of day in hospital, cost of day in ICU, ED visit, healthcare visits, surgical procedures, imaging tests, catheter placement (PICC line/central line) and microbial culture. Further detail is given in Section 4.5 of this document.

Summary statistics for total costs of care will be estimated for the pre- and post-periods for the FAS population.

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7.0 List of Potential Tables/Listings/Figures

Table shells are included in the document:
055123_ENHANCE_SAP_Table_Shells_DRAFT_v X.X_YYYYMMDD.docx.

§ Denotes output that can be produced at interim analysis. ∫ Denotes the minimum output necessary to support sample size confirmation. * Denotes output to be produced only for the sample size confirmation described in the protocol.

Table 1 Disposition of Study Patients : Enrolled Set§∫
Table 2 Patient Demographics at Baseline by All Patients: Enrolled Set§
Table 3 Comorbid Conditions Reported at Baseline: Full Analysis Set§
Table 4 Healthcare Resource Utilization at Previous 3 Months: Full Analysis Set§
Table 5.1 Infection Characteristics and Clinical Characteristics at Baseline: Full Analysis Set§
Table 5.2 Infection Characteristics and Clinical Characteristics at Day 10 to 14 Visit: Full Analysis Set§
Table 6 Use of Antibiotics by Patients During the Study: Full Analysis Set§
Table 7 Primary Outcome: Total Infection-Related LOS during Initial Care and Follow-up: Full Analysis Set§∫
Table 8 Secondary Outcomes by All Patients: Full Analysis Set§
Table 9 Secondary Outcome: Serious Adverse Events by SOC and PT: Full Analysis Set§
Table 10 Secondary Outcomes: Patient Satisfaction with Care: Full Analysis Set §
Table 11 Secondary Outcomes: Patient Work and Productivity Loss: Full Analysis Set§
Table 12 Secondary Outcomes: Patient Health-Related Quality of Life (SF-12): Full Analysis Set
Table 13 Other Outcomes: Full Analysis Set§
Table 14 Adverse Events- Overall Summary: Full Analysis Set§
Table 15 All Adverse Events by SOC and PT: Full Analysis Set§
Table 16 Adverse Events with Possible Causal Relationship to Study Drug by SOC and PT: Full Analysis Set§
Table 17 Adverse Events Leading to Study Discontinuation by SOC and PT: Full Analysis Set§
Table 18 Adverse Events Leading to Death by SOC and PT: Full Analysis Set§
Table 19 Laboratory Values: Full Analysis Set§
Table 20 Microbial Assessments: Full Analysis Set§
Table 21 Vital Signs: Full Analysis Set§
Table 22 Summary of Cost Analyses over 44 Day Period: Full Analysis Set
Table 23 Sample Size Confirmation∫*
Figure 1 Box Plot of All-Cause Hospitalization Time During Initial Care and Follow-up for Patients Completing the Study by Pre- and Post-period: Full Analysis Set
Figure 2 Box Plot of Infection-Related Hospitalization Time During Initial Care and Follow-up for Patients Completing the Study by Pre- and Post-period: Full Analysis Set
Listing 1 Patient Disposition: Enrolled Set§∫

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Listing 2 Patients Who Did Not Meet Inclusion or Exclusion Criteria: Patients Excluded from Enrolled Set §∫
Listing 3 Patient Demographics at Baseline: Enrolled Set§
Listing 4.1 Medical History at Baseline Visit: Enrolled Set, Part 1§
Listing 4.2 Medical History at Baseline Visit: Enrolled Set, Part 2§
Listing 4.3 Medical History at Baseline Visit: Enrolled Set, Part 3§
Listing 4.4 Medical History at Baseline Visit: Enrolled Set, Part 4§
Listing 5.1 Infection Characteristics: Enrolled Set, Part 1§
Listing 5.2 Infection Characteristics: Enrolled Set, Part 2§
Listing 6 Antibiotic Usage: Enrolled Set §
Listing 7 Prior Non-Antibiotic Usage for Chronic Conditions Reported at Baseline: Enrolled Set§
Listing 8 Hospitalization, ED and Observation Unit Visits: Enrolled Set §∫
Listing 9 Hospitalization Length of Stay: Enrolled Set §∫
Listing 10 Other Healthcare Visits: Enrolled Set§
Listing 11 SF-12 Questionnaire at Baseline and Day 14: Enrolled Set
Listing 12 Patient Satisfaction Survey at Day 14: Enrolled Set
Listing 13 WPAI at Day 14: Enrolled Set
Listing 14 Surgical Interventions and Procedures: Enrolled Set§
Listing 15 Adverse Events: Enrolled Set§
Listing 16 Laboratory Results: Enrolled Set§
Listing 17 Microbial Assessments: Enrolled Set§
Listing 18 Vital Signs and Physical Examination at Follow-up: Enrolled Set§

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8.0 References

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9. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care.* 1992;30(6):473-483.

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9.0 Appendices

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Appendix B: Derived Variables

Analysis Section (Visit)	Variable (Units)	Definition
General (Baseline)	Enrollment date	Informed consent date
General (Baseline)	Baseline date	Hospital admission date at initial episode of care
General (Initial Care)	Initial care indicator	If enrollment date ≤ date ≤ enrollment date + 13 days then = Yes Else = No
General (Follow-up)	Follow-up indicator	If enrollment date + 14 ≤ date ≤ enrollment date + 43 days then = Yes Else = No
Demographics (Baseline)	Age (years)	Round down to nearest integer((Initial hospital admission date – date of birth + 1)/365.25), when both dates are available.
Demographics (Baseline)	BMI	weight (kg)/ [height(m)]^2 Where necessary, height and weight will be converted to proper units.
Infection Characteristics (Baseline)	CCI	Will be scored as described in Appendix C. Includes variables for raw score and 10 year survival probability.
Infection Characteristics (Baseline)	Immunocompromised	=YES if any of the following at baseline: - Diabetes mellitus - Leukemia - Malignant lymphoma
Infection Characteristics (Baseline)	Fever	If temperature>38 ° C then =Yes Else =No
Infection Characteristics (Baseline)	SIRS Criteria Met	SIRS criteria include abnormalities in temperature, heart rate, respiration, and white blood cell count. Specifically included are:

[redacted]

Analysis Section (Visit)	Variable (Units)	Definition
		• Fever of more than> 38.0°C or hypothermia with temperature< 36.0°C • Tachycardia with heart rate > 90 beats/minute or • Tachypnea with respiratory rate of > 20 breaths/minute or $PaCO_2$ of less than 32mmHg • Abnormal white blood cell count: leukocytosis >12,000/microliter, leucopoenia <4,000/microliter, or >10% immature cells (bands).[3,4] If 2 or more criteria present = Yes Else = No
Antibiotic Medications (Initial Care and Follow-up)	Days Received Antibiotic Medication	∑ (Medication end date – Medication start date +1), when both dates are available. If dates overlap (e.g., end date and next start date are identical) then subtract 1 from summation for each occurrence.
Primary and Secondary Outcomes (All visits)	Hospitalization LOS (days)	<u>For all-cause:</u> ∑ (Hospitalization end date – Hospitalization start date +1), when both dates are available. If ongoing at end of study or discontinuation date, use study completion date or discontinuation date as end date. For outcomes, LOS will be computed two ways: only inpatient hospitalizations visits and inpatient hospitalizations visits with prolonged observation status (e.g., time in observation status exceeds 1 day). <u>For infection-related:</u>

Analysis Section (Visit)	Variable (Units)	Definition
		Subset all-cause hospitalization time for patients with infection-related hospitalization stays
Primary and Secondary Outcomes (End of Study Visit)	Completers Flag	If "Did the patient complete the study?" = 1 on the end of study visit CRF page and date of study completion does not equal missing, then =Yes, Else = No This flag will be used to repeat certain primary and secondary outcomes that could be influenced by early discontinuation (e.g., LOS)
Secondary Outcomes (Follow-up)	Response to Therapy at End of Therapy Visit	The response will be categorized as a "Complete Response" if at the day 10-14 visit there is a reduction in pain or no pain, tenderness, nor fever and the primary lesion area has reduced in size. Else, the response will be categorized as a "Partial Response" if at the day 10-14 visit there is a reduction in pain score orno pain, tenderness, nor fever and the primary lesion area remained the same size. Else, the response will be categorized as a "Failure."
Secondary Outcomes (Follow-up)	WPAI	Scores and coded variables will be derived as described in Appendix D.
Secondary Outcomes (Initial Care and Follow-up)	SF-12	SF-12 sub-scores and total scores will be compiled using the Health Outcomes Scoring Software 5.0 by QualityMetric Inc. Further detail is given in Appendix E.
Adverse Events (Baseline, Initial Care and Follow-up)	Highest severity AE	Severity of most severe AE for the patient with order of severity: Severe>Moderate>Mild Patients who only have AEs reported with missing severity,

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Analysis Section (Visit)	Variable (Units)	Definition
		highest severity AE will be reported as missing

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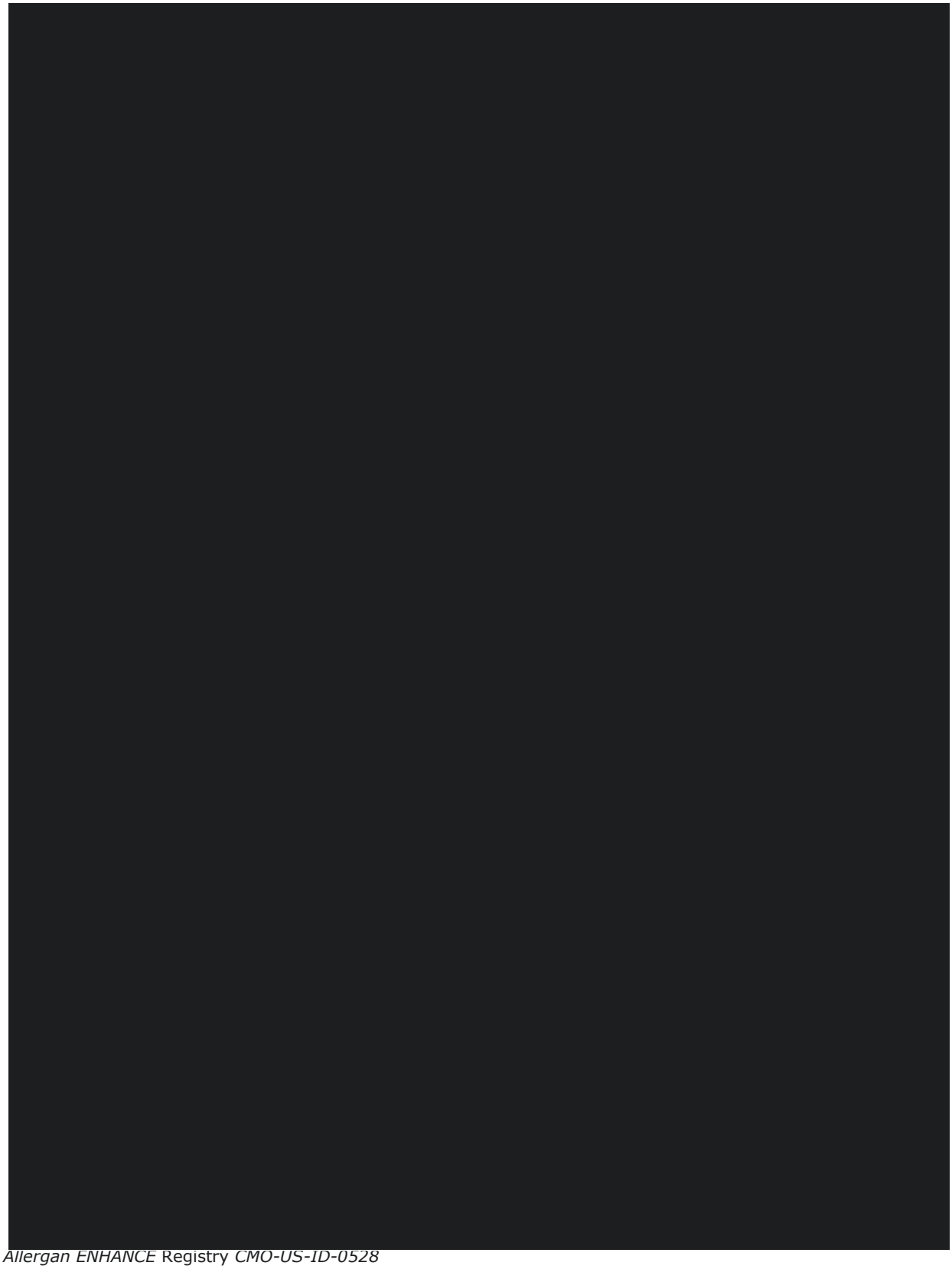

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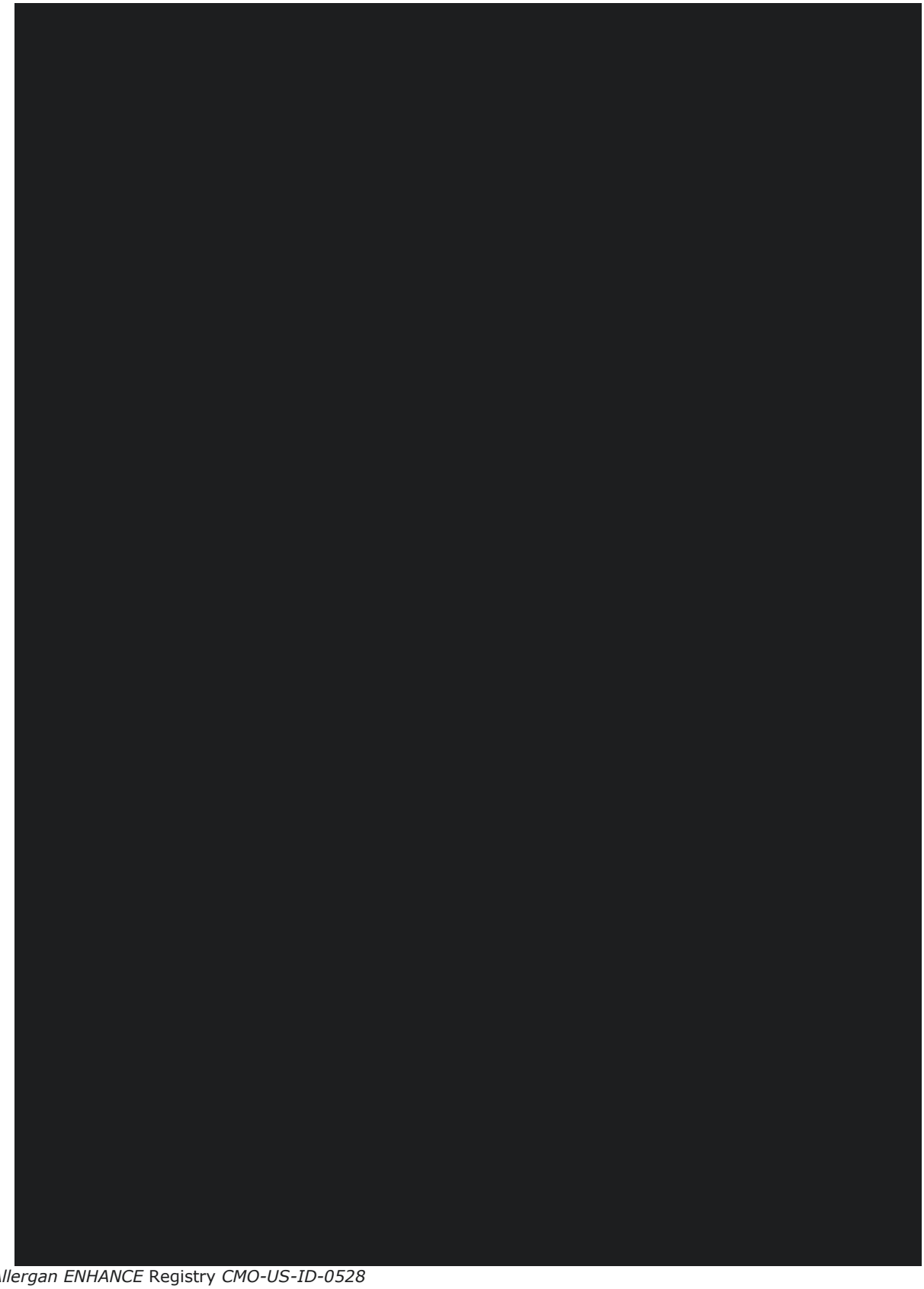

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Appendix F: Revision History

Version	Issue Date	Summary of Changes
1.0	09MAY2018	N/A (first version)

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